REMARKS

Claims 1, 38 and 41 are pending in the present application. Claims 2-37, 39, 40, and 42-54 have been cancelled. Claim 1 has been amended. No new matter has been added. The claims have been rejected for lack of utility, lack of written description, and anticipation.

IDS

Examiner states that he did not recive the references submitted to the Patent Office on September 9, 2001 and March 26, 2001. Applicants filed the references with the IDS's filed on these respective dates. Applicants have not resent these references with this Office action because of the great number of references. Upon Examiner's request, Applicants will resubmit all the references.

CLAIM OBJECTION

Claims 1-4 have been objected to for reciting non-elected SEQ ID NOs. Claims 2-4 have been cancelled so this objection is moot in regards to these claims. Claim 1 has been amended to only recite elected SEQ ID NO:8. Therefore, Applicants submit that this objection has been overcome.

CLAIM REJECTIONS

Rejections Under 35 U.S.C. § 101

Claims 1-4, 38, 41 and 50-54 have been rejected under 35 U.S.C. § 101 as lacking support by a specific and substantial credible utility. Claims 2-4 and 50-54 have been cancelled, so the rejection is moot insofar as it relates to these claims.

The Examiner alleges that the application does not disclose a specific biological role for SEQ ID NO:8 or its significance to a particular disease or disorder of physiological process. Further the Examiner asserts SEQ ID NO:8 has not been shown to be differentially expressed in any disease or disorder and cannot be employed in a diagnostic capacity. Therefore, according to the Examiner, the specification does not disclose a credible, substantial and specific "real world" use for SEQ ID NO:8. Applicants traverse for the reasons described below.

The requirements for satisfying the utility requirement are explained in the Manual of Patent Examination Practice (MPEP) 8th Edition, which states that only one credible assertion of specific and substantial utility, need be specified for an invention:

Specific Utility

> A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. *Knapp v. Anderson*, 477 F.2d 588, 177 USPQ 688 (CCPA 1973).

Substantial Utility

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. Section 2107.01

Applicants submit that at least one substantial and specific utility exists for the claimed invention and is readily apparent based on the teachings of the specification. Applicants respectfully assert that the claimed protein, SEQ ID NO:8, is homologous to an olfactory receptor protein and is useful, *inter alia*, as a marker (prognostic indicator) or therapy (therapeutic) for cancers such as lung and kidney cancers, thereby demonstrating a "real world" use and patentable utility (*See,* specification at page 3, lines 5 to page 7, line -18, and Exhibit A, attached hereto).

In Exhibit A, included herewith, the tables depict the scaled results of quantitative gene expression analyses performed using SEQ ID NO:8 with gene-specific primers that measure the

relative SEQ ID NO:8 expression levels in normal cells or tissues, stimulated cells, or pathological tissue samples. The Relative Expression Score for each sample indicates the relative quantity of a SEQ ID NO:8 transcript, with 0.0 indicating no detectable expression and 100.00 indicating highest detectable expression level.

Exhibit A shows that SEQ ID NO:8 is highly expressed in various tissues but a significant distinction in expression is observed between matched samples of a patient's normal lung tissue and malignant lung tissue, and normal renal tissue and malignant renal tissue. (*See*, Table AL Panel 2D). These results demonstrate that SEQ ID NO:8 is proximally linked to normal cell physiology and pathophysiological events such as lung and renal cancer. Therefore, one of skill in the art, would utilize SEQ ID NO:8 for example, in screens for effective therapeutics which modulate the activity, latency or predisposition to human airway epithelial disorders. Further, SEQ ID NO:8 has utility as a treatment for preventing or alleviating a disorder by administration of the gene, gene product or antibodies thereto to a subject which has conditions associated with dysregulation of the gene. SEQ ID NO:8 can also be used to diagnose lung and renal cancers.

Applicants assert that the specification and accompanying Exhibit A identifies a disease/disorder associated with SEQ ID NO:8, shows differential expression of the protein in the disease/disorder and associates the protein with a physiological process, which one would wish to manipulate for clinical effect. Consistent with the teachings of the specification and the utilities known by those of ordinary skill in the art, Applicants respectfully submit that it would be clear to the skilled artisan that the polypeptide of the present invention (SEQ ID NO:8) is useful as a marker or therapy for diseases or disorders such as human lung and renal disorders and thus have a credible, specific and substantial utility. Applicants thus respectfully request withdrawal of the rejection under 35 U.S.C. §101.

Rejections under U.S.C. § 112, first paragraph

Claims 1-4, 38, 41 and 50-54 were rejected under 35 U.S.C. § 112, first paragraph because one skilled in the art would not know how to use the invention since the claimed invention lacks utility. As discussed above, throughout the specification and Exhibit A, Claims 1, 38 and 41 have a specific, substantial, and credible utility. Since the claims have been demonstrated to have such utility, Applicants submit that this rejection should be withdrawn.

Claims 1-4, 38, 41, and 50-54 were also rejected under 35 U.S.C. § 112, first paragraph for lack of written description. Claims 2-4 and 50-54 have been cancelled, so the rejection is moot insofar as it relates to these claims. Examiner alleges that the specification contains no description of a mature or variant form of SEQ ID NO:8. Further, Examiner alleges that the instant specification does not identify those structural features in SEQ ID NO:8 which are found only in the genus of proteins defined by the structural limitations of these claims.

To facilitate prosecution, Applicants have amended claim 1 to remove any reference to variants of any kind. Therefore, Applicants request that this rejection be withdrawn.

Rejections under U.S.C.§ 102(a)

Claim 1 was rejected under 35 U.S.C. § 102(a),for being anticipated by Oohashi et al., which discloses a polypeptide that shares 98.2% identity with SEQ ID NO:8. Applicants have amended claim 1 as mentioned above to read on only an amino acid sequence comprising SEQ ID NO:8. Oohashi et al. does not disclose such a sequence. Therefore, Applicants request that this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Exhibit A

The quantitative expression of various clones was assessed using microtiter plates containing RNA samples from a variety of normal and pathology-derived cells, cell lines and tissues using real time quantitative PCR (RTQ PCR). RTQ PCR was performed on an Applied Biosystems ABI PRISM® 7700 or an ABI PRISM® 7900 HT Sequence Detection System. Various collections of samples are assembled on the plates, and referred to as Panel 1 (containing normal tissues and cancer cell lines), Panel 2 (containing samples derived from tissues from normal and cancer sources), Panel 3 (containing cancer cell lines), Panel 4 (containing cells and cell lines from normal tissues and cells related to inflammatory conditions), Panel 5D/5I (containing human tissues and cell lines with an emphasis on metabolic diseases), AI_comprehensive_panel (containing normal tissue and samples from autoinflammatory diseases), Panel CNSD.01 (containing samples from normal and diseased brains) and CNS_neurodegeneration_panel (containing samples from normal and Alzheimer's diseased brains).

RNA integrity from all samples is controlled for quality by visual assessment of agarose gel electropherograms using 28S and 18S ribosomal RNA staining intensity ratio as a guide (2:1 to 2.5:1 28s:18s) and the absence of low molecular weight RNAs that would be indicative of degradation products. Samples are controlled against genomic DNA contamination by RTQ PCR reactions run in the absence of reverse transcriptase using probe and primer sets designed to amplify across the span of a single exon.

First, the RNA samples were normalized to reference nucleic acids such as constitutively expressed genes (for example, β-actin and GAPDH). Normalized RNA (5 ul) was converted to cDNA and analyzed by RTQ-PCR using One Step RT-PCR Master Mix Reagents (Applied Biosystems; Catalog No. 4309169) and gene-specific primers according to the manufacturer's instructions.

In other cases, non-normalized RNA samples were converted to single strand cDNA (sscDNA) using Superscript II (Invitrogen Corporation; Catalog No. 18064-147) and random hexamers according to the manufacturer's instructions. Reactions containing up to 10 μg of total RNA were performed in a volume of 20 μl and incubated for 60 minutes at 42°C. This reaction can be scaled up to 50 μg of total RNA in a final volume of 100 μl. sscDNA samples are then normalized to reference nucleic acids as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions.

Probes and primers were designed for each assay according to Applied Biosystems Primer Express Software package (version I for Apple Computer's Macintosh Power PC) or a similar algorithm using the target sequence as input. Default settings were used for reaction conditions and the following parameters were set before selecting primers: primer concentration = 250 nM, primer melting temperature (Tm) range = 58°-60°C, primer optimal Tm = 59°C, maximum primer difference = 2°C, probe does not have 5'G, probe Tm must be 10°C greater than primer Tm, amplicon size 75bp to 100bp. The probes and primers selected (see below) were synthesized by Synthegen (Houston, TX, USA). Probes were double purified by HPLC to remove uncoupled dye and evaluated by mass spectroscopy to verify coupling of reporter and quencher dyes to the 5' and 3' ends of the probe, respectively. Their final concentrations were: forward and reverse primers, 900nM each, and probe, 200nM.

PCR conditions: When working with RNA samples, normalized RNA from each tissue and each cell line was spotted in each well of either a 96 well or a 384-well PCR plate (Applied Biosystems). PCR cocktails included either a single gene specific probe and primers set, or two multiplexed probe and primers sets (a set specific for the target clone and another gene-specific set multiplexed with the target probe). PCR reactions were set up using TaqMan® One-Step RT-PCR Master Mix (Applied Biosystems, Catalog No. 4313803) following manufacturer's instructions. Reverse transcription was performed at 48°C for 30 minutes followed by amplification/PCR cycles as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) using a log scale, with the difference in RNA concentration between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. The percent relative expression is then obtained by taking the reciprocal of this RNA difference and multiplying by 100.

When working with sscDNA samples, normalized sscDNA was used as described previously for RNA samples. PCR reactions containing one or two sets of probe and primers were set up as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions. PCR amplification was performed as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were analyzed and processed as described previously.

Panels 2D, 2.2, 2.3 and 2.4

The plates for Panels 2D, 2.2, 2.3 and 2.4 generally include 2 control wells and 94 test samples composed of RNA or cDNA isolated from human tissue procured by surgeons working in close cooperation with the National Cancer Institute's Cooperative Human Tissue Network (CHTN) or the National Disease Research Initiative (NDRI) or from Ardais or Clinomics). The tissues are derived from human malignancies and in cases where indicated many malignant tissues have "matched margins" obtained from noncancerous tissue just adjacent to the tumor. These are termed normal adjacent tissues and are denoted "NAT" in the results below. The tumor tissue and the "matched margins" are evaluated by two independent pathologists (the surgical pathologists and again by a pathologist at NDRI/ CHTN/Ardais/Clinomics). Unmatched RNA samples from tissues without malignancy (normal tissues) were also obtained from Ardais or Clinomics. This analysis provides a gross histopathological assessment of tumor differentiation grade. Moreover, most samples include the original surgical pathology report that provides information regarding the clinical stage of the patient. These matched margins are taken from the tissue surrounding (i.e. immediately proximal) to the zone of surgery (designated "NAT", for normal adjacent tissue, in Table RR). In addition, RNA and cDNA samples were obtained from various human tissues derived from autopsies performed on elderly people or sudden death victims (accidents, etc.). These tissues were ascertained to be free of disease and were purchased from various commercial sources such as Clontech (Palo Alto, CA), Research Genetics, and Invitrogen.

A. SEQ ID NO:8: 10129612.0.405, submitted to study DDAT on 12/13/00 by rpoach; classification type=Legacy; novelty=D; ORF start=280, ORF stop=8478, frame=1; 9826 bp.

Expression of gene SEQ ID NO:8 was assessed using the primer-probe set Ag047 described in Table AG. Results of the RTQ-PCR runs are shown in Table AL.

Table AG. Probe Name Ag047

Primers	Sequences	Length	Start Position
Forward	5'-ccaatgacctggccacca-3'	18	1145
Probe	TET-5'-ccagagtccgttcagcttcaggacagc-3'-TAMRA	27	1165
Reverse	5'-gtggcacgttgctgtttagc-3'	20	1197

Table AL. Panel 2D

Column A - Rel. Exp.(%) Ag047, Run 144771648 Column B - Rel. Exp.(%) Ag047, Run 152940364					
Tissue Name	**A**	**B**	**Tissue Name**	**A**	**B**
Normal Colon	5.5	8.9	Kidney Margin 8120608	3.4	0.8
CC Well to Mod Diff (ODO3866)	1.4	0.2	Kidney Cancer 8120613	0.4	0.8
CC Margin (ODO3866)	0.4	0.5	Kidney Margin 8120614	2.8	1.2
CC Gr.2 rectosigmoid (ODO3868)	0.4	0.1	Kidney Cancer 9010320	76.8	39.0
CC Margin (ODO3868)	2.5	0.9	Kidney Margin 9010321	10.4	5.1
CC Mod Diff (ODO3920)	0.0	0.0	Normal Uterus	0.0	0.2
CC Margin (ODO3920)	0.7	0.9	Uterus Cancer 064011	0.9	0.0
CC Gr.2 ascend colon (ODO3921)	0.0	0.7	Normal Thyroid	0.3	0.0
CC Margin (ODO3921)	0.2	0.2	Thyroid Cancer 064010	0.0	0.0
CC from Partial Hepatectomy (ODO4309) Mets	0.6	0.4	Thyroid Cancer A302152	1.4	0.1
Liver Margin (ODO4309)	11.1	13.6	Thyroid Margin A302153	1.7	0.9
Colon mets to lung (OD04451-01)	0.0	0.4	Normal Breast	20.3	5.7
Lung Margin (OD04451-02)	1.3	1.0	Breast Cancer (OD04566)	0.3	0.1
Normal Prostate 6546-1	19.1	0.7	Breast Cancer (OD04590-01)	2.4	2.2
Prostate Cancer (OD04410)	5.8	2.9	Breast Cancer Mets (OD04590-03)	0.7	0.1
Prostate Margin (OD04410)	4.7	5.7	Breast Cancer Metastasis (OD04655-05)	6.9	3.3
Prostate Cancer (OD04720-01)	2.9	3.3	Breast Cancer 064006	5.6	8.3
Prostate Margin (OD04720-02)	12.5	10.7	Breast Cancer 1024	47.0	19.3
Normal Lung 061010	1.5	2.7	Breast Cancer 9100266	14.9	9.3
Lung Met to Muscle (ODO4286)	0.3	0.1	Breast Margin 9100265	4.6	1.5
Muscle Margin (ODO4286)	0.3	0.2	Breast Cancer A209073	48.3	12.9
Lung Malignant Cancer (OD03126)	0.4	0.2	Breast Margin A209073	38.7	16.6
Lung Margin (OD03126)	0.4	1.0	Normal Liver	0.2	0.1
Lung Cancer (OD04404)	86.5	**100.0**	Liver Cancer 064003	11.8	5.6

Lung Margin (OD04404)	18.3	3.3	Liver Cancer 1025	4.5	1.6
Lung Cancer (OD04565)	**100.0**	52.1	Liver Cancer 1026	6.2	6.7
Lung Margin (OD04565)	0.2	0.1	Liver Cancer 6004-T	15.6	3.3
Lung Cancer (OD04237-01)	6.3	1.5	Liver Tissue 6004-N	0.1	0.2
Lung Margin (OD04237-02)	1.4	0.5	Liver Cancer 6005-T	14.6	8.0
Ocular Mel Met to Liver (ODO4310)	0.4	0.3	Liver Tissue 6005-N	6.4	7.0
Liver Margin (ODO4310)	2.3	1.8	Normal Bladder	1.3	0.9
Melanoma Mets to Lung (OD04321)	0.0	0.3	Bladder Cancer 1023	0.4	0.2
Lung Margin (OD04321)	2.1	2.6	Bladder Cancer A302173	7.5	5.3
Normal Kidney	6.7	4.9	Bladder Cancer (OD04718-01)	27.7	23.0
Kidney Ca, Nuclear grade 2 (OD04338)	0.0	0.0	Bladder Normal Adjacent (OD04718-03)	0.4	0.3
Kidney Margin (OD04338)	3.5	1.5	Normal Ovary	1.4	0.4
Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	0.1	Ovarian Cancer 064008	1.3	0.5
Kidney Margin (OD04339)	18.4	10.3	Ovarian Cancer (OD04768-07)	0.4	0.2
Kidney Ca, Clear cell type (OD04340)	0.0	0.8	Ovary Margin (OD04768-08)	1.0	0.8
Kidney Margin (OD04340)	6.5	4.4	Normal Stomach	4.3	2.0
Kidney Ca, Nuclear grade 3 (OD04348)	90.8	36.1	Gastric Cancer 9060358	2.4	0.7
Kidney Margin (OD04348)	4.6	3.2	Stomach Margin 9060359	0.0	0.0
Kidney Cancer (OD04622-01)	2.7	1.8	Gastric Cancer 9060395	0.9	2.0
Kidney Margin (OD04622-03)	2.0	0.2	Stomach Margin 9060394	0.2	0.3
Kidney Cancer (OD04450-01)	0.0	0.0	Gastric Cancer 9060397	0.4	0.5
Kidney Margin (OD04450-03)	3.1	1.4	Stomach Margin 9060396	0.0	0.1
Kidney Cancer 8120607	1.5	0.3	Gastric Cancer 064005	0.7	0.7

Results:

Results show strong association of this gene with various cancers. Panel 2D shows gene expression was higher in gastric, bladder, lung and kidney cancer specimens than in the normal adjacent tissue. Expression of this gene is associated with these forms of cancer and therefore can be used for cancer detection, identification, diagnosis and furthermore, therapeutic modulation of this gene might be of use in the treatment of cancer.